

WHAT IS CLAIMED IS:

1. A method for inducing tolerance in a mammal to a pre-selected antigen comprising the steps of
 - a. isolating peripheral blood mononuclear cells (PBMC) from a whole blood sample from said mammal;
 - b. isolating dendritic cells from said PBMC;
 - c. exposing said dendritic cells *ex vivo* to apoptotic cells expressing said pre-selected antigen in the presence of at least one dendritic cell maturation stimulatory molecule and in the absence of effective CD4+ T cell help;
 - d. introducing a cellular portion of step c) into said mammal;wherein said dendritic cells induce apoptosis of antigen-specific CD8+ T cells in said mammal resulting in tolerance to said antigen.
2. The method of claim 1 wherein said dendritic cell maturation stimulatory molecule is PGE2, TNF-alpha, lipopolysaccharide, monocyte conditioned medium, CpG-DNA, or any combination thereof.

- 1 3. The method of claim 1 wherein said absence of effective CD4+ T cell is achieved by
2 excluding CD4+ T cells from said step c).
3
- 4 4. The method of claim 1 wherein said absence of effective CD4+ T cell help is achieved by
5 including in step c) at least one agent that inhibits or eliminates effective CD4+ T cell
6 help.
7
- 8 5. The method of claim 4 wherein said agent which inhibits or eliminates effective CD4+
9 help is a monoclonal antibody to a TNF superfamily member, a combination thereof, a
10 monoclonal antibody to a receptor for a TNF superfamily member, or a combination
11 thereof
12
- 13 6. The method of claim 5 wherein said TNF superfamily member is CD40L, TRANCE,
14 OX40 or DR3.
15
- 16 7. The method of claim 5 wherein said receptor for a TNF superfamily member is CD40,
17 TRANCE, OX40 ligand or TWEAK.
18
- 19 8. The method of claim 1 wherein said absence of effective CD4+ T cell is achieved by
20 inhibiting formation of mature forms of MHC II / peptide complexes within the dendritic
21 cell.
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- 1 9. The method of claim 8 wherein said inhibiting is achieved by preventing cleavage of
2 invariant chain.
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- 4 10. The method of claim 9 wherein said preventing is achieved by addition of a cathepsin
5 inhibitors.
6
- 7 11. The method of claim 8 wherein said inhibiting is achieved by blocking loading of
8 peptides by inhibiting HLA-DM.
9
- 10 12. The method of claim 8 wherein said inhibiting is achieved by preventing successful
11 antigen degradation and formation of a MHC II peptide epitope.
12
- 13 13. The method of claim 12 wherein said preventing is achieved by inhibiting cathepsin D or
14 alternative proteases.
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- 16 14. The method of claim 8 wherein said inhibiting is achieved by inhibiting transport of
17 MHC II / peptide complexes to the cells surface.
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- 19 15. The method of claim 4 wherein said agent which inhibits or eliminates effective CD4 T
20 cell help inhibits signalling consequent to dendritic cell-CD4 T cell engagement.
21
- 22 16. The method of claim 15 wherein said agent is selected from a FKBP antagonist and a
23 TOR antagonist.

- 1 17. The method of claim 16 wherein said FKBP antagonist is FK-506.
- 2
- 3 18. The method of claim 16 wherein said TOR antagonist is rapamycin.
- 4
- 5 19. The method of claim 1 wherein said pre-selected antigen is a tumor antigen, a viral
- 6 antigen, a self antigen or a transplant antigen.
- 7
- 8 20. The method of claim 4 wherein said presence of at least one agent that inhibits effective
- 9 CD4 T cell help comprises a monoclonal antibody to TRANCE and FK-506.
- 10
- 11 21. The method of claim 1 wherein after a period of time following step c), a cellular portion
- 12 is infused into the mammal.
- 13
- 14 22. The method of claim 1 wherein said mammal is a human.
- 15
- 16 23. A method for inducing tolerance in a mammal to a pre-selected antigen comprising the
- 17 steps of
- 18 a. providing a dendritic cell chemoattractant at a site in a mammalian body, said
- 19 site comprising an antigen to which tolerization of an immune response is desired or
- 20 made to comprise an antigen to which tolerization of an immune response is desired
- 21 by administration of said antigen to said site; and
- 22

1 b. administering to said site or systemically to said mammal an agent which
2 inhibits or eliminates effective CD4+ T cell help;

3
4 wherein immune system cells of said mammal are tolerized to said antigen.

5
6 24. The method of claim 23 wherein said dendritic cell chemoattractant is a ligand for
7 CCR6.

8
9 25. The method of claim 23 wherein said ligand for CCR6 is 6-C-kine.

10
11 26. The method of claim 23 wherein said agent which inhibits or eliminates effective
12 CD4+ help is a monoclonal antibody to a TNF superfamily member, a combination
13 thereof, a monoclonal antibody to a receptor for a TNF superfamily member, or a
14 combination thereof.

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16 27. The method of claim 26 wherein said TNF superfamily member is CD40L,
17 TRANCE, OX40 or DR3.

18
19 28. The method of claim 26 wherein said receptor for a TNF superfamily member is
20 CD40, TRANCE, OX40 ligand or TWEAK.

29. The method of claim 23 wherein said agent which inhibits or eliminates effective CD4+ T cell inhibits formation of mature forms of MHC II / peptide complexes within the dendritic cell.

30. The method of claim 29 wherein said inhibits formation is achieved by preventing cleavage of invariant chain.

31. The method of claim 29 wherein said inhibits or eliminates is achieved by addition of a cathepsin inhibitor.

32. The method of claim 29 wherein said inhibiting is achieved by blocking loading of peptides by inhibiting HLA-DM.

33. The method of claim 32 wherein said inhibiting is achieved by preventing successful antigen degradation and formation of a MHC II peptide epitope.

34. The method of claim 33 wherein said preventing is achieved by inhibiting cathepsin D or alternative proteases.

35. The method of claim 29 wherein said inhibiting is achieved by inhibiting transport of MHC II / peptide complexes to the cells surface.

36. The method of claim 23 wherein said agent which inhibits or eliminates effective CD4 T cell help inhibits signalling consequent to dendritic cell-CD4 T cell engagement.

37. The method of claim 36 wherein said agent is selected from a FKBP antagonist and a TOR antagonist.

38. The method of claim 37 wherein said FKBP antagonist is FK-506.

39. The method of claim 37 wherein said TOR antagonist is rapamycin.

40. The method of claim 23 wherein said pre-selected antigen is a tumor antigen, a viral antigen, a self antigen or a transplant antigen.

41. The method of claim 23 wherein said presence of at least one agent that inhibits effective CD4 T cell help comprises a monoclonal antibody to TRANCE and FK-506.